REMARKS

Claims 1-36 were pending in this application. Claims 5-12, 23-27, and 34-35 have been canceled without prejudice as being drawn to a non-elected invention. Claim 36 has also been canceled and claims 1-4, 13-17, 22, 28, and 29 have been amended. Accordingly, upon entry of the amendments presented herein, claims 1-4, 13-22, and 28-33 will remain pending in the application.

Support for the amendments to the claims may be found throughout the specification and claims as originally filed. Specifically, support for the amendments to claims 1-4, 16, and 17 may be found at, for example, page 11, lines 25-27 and page 13, lines 13-22 of the specification; and support for the amendments to claim 22 may be found at, for example, page 16, lines 28-36, page 59, lines 29.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election/Restriction

Group I (claims 1-4, 13-22, 28-33, and 36) directed to methods of determining whether a subject has an bone marrow derived stem cell dependent metaplasia, comprising detecting the presence of BMDC polypeptide, was elected by Applicants with traverse. Applicants acknowledge the indication in the Office Action that the restriction requirement has been deemed to be proper and has, therefore, been made final. Accordingly, claims 5-12, 23-27, and 34-35 have been canceled as being directed to a non-elected invention.

Title

The Office Action states that the title of the invention is not descriptive and requires a new title "clearly indicative of the invention *to which the claims are directed.*"

Applicants respectfully submit that the amendment to the Title presented herein clearly indicates the invention to which the claims are directed, *i.e.,* the prognosis and diagnosis of bone

marrow derived stem cell associated cancer and bone marrow derived stem cell dependent metaplasia. Accordingly, Applicants request reconsideration and withdrawal of the objection to the title.

Information Disclosure Statement

Applicants acknowledge the indication in the Office Action that the "international Search Reports on the IDS, filed 06/31/06 has been considered, however said citation has been crossed out as it is not appropriate for printing in an issued patent."

Rejections of Claims 16-20 and 22 Under 35 U.S.C. §112, Second Paragraph

The Office Action has rejected claims 16-20 and 22 under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

With respect to claim 16, the Office Action states that

> [d]ependent claim 16 recites "the level of BMDC or BMDC-derived cells". There is insufficient antecedent basis for this limitation in the claims, since base Claim 1 does not recite levels of BMDC or BMDC-derived cells.

Applicants respectfully submit that, without acquiescing to the validity of the foregoing rejection and solely in the interest of expediting prosecution, the amendments to claim 16 presented herein render the rejection of claim 16 moot. In particular, claim 16 has been amended to recite "the ***presence*** of the MSC or MSC derived cell". Accordingly, Applicants respectfully request that the rejection of claim 16 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

With respect to claim 22, the Office Action states that

> [c]laim 22 is indefinite and ambiguous in the recitation of Flk-l, Sca-l *etc* polypeptide in the second line. Recitation of a polypeptide without providing SEQ ID NO for the polypeptide is indefinite and ambiguous

> because different laboratories may have the same name for a different polypeptide.

Applicants respectfully traverse the foregoing objection. The terms "Flk-1", "Sca-1", "Thy-1", "KRT1-19", "TFF2", "Patched", and "CXL4" are art-recognized terms and accordingly, a person of ordinary skill in the art, at the time of filing the present application, would recognize and understand the meaning of the terms "Flk-1", "Sca-1", "Thy-1", "cytokeratin 19", "TFF2", "Patched", and "CXCR4"without further definition. For example, a PubMed search conducted by Applicants revealed 432 publications, published prior to Applicants' priority date, that recite the term "Flk-1"; approximately 4, 000 publications, published prior to Applicants' priority date, that recite the term "Sca-1"; approximately 4, 000 publications, published prior to Applicants' priority date, that recite the term "Thy-1"; 535 publication, published prior to Applicants' priority date, that recite the term "cytokeratin"; 63 publications, published prior to Applicants' priority date, that recite the term "TFF2"; 889 publications, published prior to Applicants' priority date, that recite the term "Patched"; and 1, 536 publications, published prior to Applicants' priority date, that recite the term "CXCR4". Moreover, at page 16, lines 28-36 of the specification, Applicants teach the accession numbers of these polypeptides such that one of skill in the art could readily identify any aliases as well as the sequence of the polypeptide. Thus, Applicants submit that the recitation of the terms "Flk-1", "Sca-1", "Thy-1", "cytokeratin 19", "TFF2", "Patched", and "CXCR4" is clear and definite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-4, 13-22, 28-33, and 36 Under 35 U.S.C. §112, First Paragraph

The Office Action has rejected claims 1-4, 13-22, 28-33, and 36 under 35 U.S.C. 112 § first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

In particular, the Office Action states that

> Applicant has not provided sufficient guidance to enable one skill in the art to use claimed (i) a method of determining whether a subject has an

> BMDC dependent metaplasia, claimed in claim 1, or a method of determining whether a subject has BMDC-associated cancer, claimed in claim 2 or a subject has a higher than normal risk of development an BMDC dependent metaplasia, claimed in claim 3 or BMDC-associated cancer, claimed in claim 4, each comprising detecting the presence of BMDC or BMDC-derived cells in the test sample from the subject in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.
>
> In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

With respect to the amount of direction or guidance provided in the specification and the presence or absence of working example, the Office Action states that

> [t]he specification only discloses that: (i) BMDC are involved in healing of acute gastric ulcers (see Example 1 in particular), (ii) inflammation and tissue loss secondary to chronic gastric *Helicobacter* infection represent a sufficient stimulus for long-term engraftment and homing of BMDC that might contribute over time to metaplasia, dysplasia and cancer(see Example 2 and 3 in particular). It is noted however, that specification disclosed that "***in our system we believed*** that MSC is the most likely cell type responsible for engraftment seen (emphases added, see page 61 in particular). The Specification farther disclosed that it is suggested that the quality as well as the quantity and duration of inflammation plays a central role in the degree of maladaptive differentiation of the BMDC once it resides in the peripheral tissue. ***The concept that cancer can arise from BMDC*** would alter greatly our understanding of cancer initiation and progression (emphases added). In other words, the Specification only *prophetically* suggested that MBDC might contribute to cancer. (Emphasis added).
>
> ***The specification does not adequately conformed or show the existence of direct correlation between the presence of BMDC or BMDC -derived cells and probability that the subject has BMDC-associated cancer or BMDC dependent metaplasia.*** The Specification provide no evidences that the presence of BMDC or BMDC-derived cells in a test sample from the subject is an indicative that the subject has BMDC-associated cancer or BMDC dependent metaplasia or has a higher than normal risk of developing either an BMDC-dependent metaplasia or BMDC-associated cancer. ***Moreover, no animals models were used to***

> ***study the effectively of a method*** of determining whether a subject has an BMDC dependent metaplasia or a method of determining whether a subject has BMDC-associated cancer or a subject has a higher than normal risk of development an BMDC dependent metaplasia or BMDC-associated cancer, each comprising detecting the presence of BMDC or BMDC-derived cells in the test sample from the subject. (Emphasis added).

Applicants respectfully traverse the foregoing rejection for at least the following reasons. Claim 1, as amended, and claims dependent therefrom, are directed to methods of determining whether a subject has a bone marrow derived stem cell (BMDC) dependent metaplasia, comprising ***detecting the presence of a mesenchymal stem cell (MSC) or MSC derived cell in a test sample from the subject, wherein the presence of the MSC or MSC derived cell is indicative that the subject is afflicted with BMDC-dependent metaplasia***. Claim 2, as amended, and claims dependent therefrom, are directed to methods of determining whether a subject has a bone marrow derived stem cell (BMDC) associated cancer comprising ***detecting the presence of a mesenchymal stem cell (MSC) or MSC derived cell in a test sample from the subject, wherein the presence of the MSC or MSC derived cell is indicative that the subject is afflicted with BMDC associated cancer***. Claim 3, as amended, and claims dependent therefrom, are directed to methods of determining whether a subject has a higher than normal risk of developing a bone marrow derived stem cell (BMDC) dependent metaplasia, comprising ***detecting the presence of a mesenchymal stem cell (MSC) or MSC derived cell in a test sample from the subject, wherein the presence of the MSC or MSC derived cell is indicative that the subject is at higher than normal risk of developing BMDC dependent metaplasia***. Claim 4, as amended, and claims dependent therefrom, are directed to methods of determining whether a subject has a higher than normal risk of developing a bone marrow derived stem cell (BMDC) associated cancer comprising ***detecting the presence of a mesenchymal stem cell (MSC) or MSC derived cell in a test sample from the subject, wherein the presence of the MSC or MSC derived cell is indicative that the subject is at higher than normal risk of developing BMDC associated cancer***. Applicants submit that, based on the teachings in Applicants' specification and the knowledge generally available in the art at the time of the invention, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation.

In contrast to the assertions set forth in the Office Action, the scope of the claims is commensurate with the disclosure in Applicants' specification. In particular, Applicants specification is based on the ***novel discovery that the loss of cells in inflamed tissue during chronic inflammation leads to the influx and long-term re-population of the tissue with bone marrow stem cells or bone marrow derived stem cells (BMDC), and that it is these stem cells that are the primary source of metaplasia and cancer***. More specifically, Applicants have discovered that it is a specific population of BMDCs, mesenchymal or mesenchymal derived cells (MSC), that are the primary source of metaplasia and cancer (see, *e.g.,* Example I, especially, page 57, line 1, through page 61, lines 1-2 of the specification). This was a surprising discovery in that, as known in the art and taught in Applicants' specification, mesenchymal stem cells normally only form chondrocytes and osteoblasts, while hematopoietic stem cells (HSC), the other specific population of BMDCs, are much more totipotent and give rise to cells of the blood and immune system (*e.g.*, erythroid, granulocyte/macrophage, magakaryocite and lymphoid lineages), cells of the liver (including hepatocytes, bile duct cells), lung, kidney (*e.g.*, renal tubular epithelial cells and renal parenchyma), gastrointestinal tract, skeletal muscle fibers, astrocytes of the CNS, Purkinje neurons, cardiac muscle (*e.g.*, cardiomyocytes), endothelium and skin (see, *e.g.,* page 11, lines12-23 of the specification).

Accordingly, Applicants' specification is directed to ***methods for diagnosing and prognosing BMDC dependent metaplasia and/or BMDC associated cancer by detecting the presence of MSC or MSC derived cells***. Applicants point the Examiner to page 16, line 15, through page 28, lines 1-17 of the specification where Applicants teach a plethora of art known diagnostic and prognostic methods, *i.e.,* immunological based and nucleic acid based methods, such as radioimmunoassay, immunoradiometric assays, ELISAs, and numerous PCR-based assays, each of which is suitable for practicing the methods of the invention.

Applicants also submit that the specification provides ***working examples*** (and not prophetic examples as asserted in the Office Action at page 4) using an art recognized mouse model of cancer, *e.g.,* gastric adenocarcinoma (*Helicobacter* infection of C57BL//*6JGtrosa26* (ROSA 26) mice), which ***establish a correlation between the presence of BMDC and cancer/metaplasia.*** In particular, Applicants point the Examiner to Example 1 of the specification which teaches that in this animal model of gastric adenocarcinoma, BMDC home

to, engraft, and progress over time to metaplasia, dysplasia, and cancer using three distinct methodologies. See, *e.g.,* Example 1, page 57, lines 30-38.

Moreover, with respect to the assertions that the pending claims are not enabled because, Applicants do not "show the existence of direct correlation between the presence of BMDC or BMDC -derived cells and probability that the subject has BMDC-associated cancer or BMDC dependent metaplasia" and that "no animal models were used to study the effective[ness]" of the claimed methods, Applicants submit that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether a working example is disclosed and an example may be a working example or a prophetic example (M.P.E.P. 2164.02). Furthermore, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

Accordingly, even assuming *arguendo*, that the animal models of cancer utilized in the working examples of Applicants' specification are not sufficiently predictive, as asserted by the Examiner, is an insufficient basis to conclude that the present invention is non-enabled, as is the fact that Applicants do not provide any *subjects*. (MPEP2164.02). Thus, the present application provides an amount of guidance to one of skill in the art as to how to practice the methods of the invention which is commensurate in scope with the claims. Thus, the present application provides an amount of guidance to one of skill in the art as to how to practice the methods of the invention which is commensurate in scope with the claims.

With respect to the predictability in the art, the Office Action states that

> [s]ince there is no animal model studies and data in the specification to show the effectively of a method of determining whether a subject has an BMDC dependent metaplasia or a method of determining whether a subject has BMDC-associated cancer or a subject has a higher than normal risk of development either an BMDC dependent metaplasia or BMDC-associated cancer, each comprising detecting the presence of BMDC or BMDC-derived cells in the test sample from the subject it is unpredictable how to correlate disclosed data with the claimed intended use. Lyden et al., (Nature Medicine, 2001, Vol.7, page 1194-1201) teach that it is not yet established whether BM-derived precursor cells can contribute to tumor neo-angiogenesis (see entire document, Abstract in particular). Feldman *et al* (*Transplant. Proc.* 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease,

> leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Mestas *et al* (*J. of Immunology*, 2004,172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans.

With respect to the Examiner's assertions regarding the "constraints" associated with the use of animal models of disease, Applicants submit that while some aspects of the use of animal models to study human disease may be controversial, methods for the detection of specific cell types (*i.e.,* MSC and MSC derived cells) in a sample, (including immunological and nucleic acid based methods), are well-established, routine to one of skill in the art, and exemplified in the working examples of the instant specification (discussed above). Moreover, the fact that Applicants findings were "unexpected" does not mean that the claimed methods are not enabled as being unpredictable. Accordingly, Applicants submit that an ordinary skilled artisan would be able to practice the claimed invention using only routine experimentation.

Furthermore, Applicants submit that the invention must be given the presumption of correctness and operativeness. As set forth in *In re Marzocchi*, 439 F.2d 220,

> [a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112.

In view of all of the foregoing, Applicants further submit that based on the teachings and guidelines of the present invention as disclosed in the application, in combination with the knowledge of one of skill in the art at the time the application was filed, methods for determining whether a subject has a BMDC dependent metaplasia, and/or a BMDC associated cancer, and/or whether a subject has a higher than normal risk of developing a BMDC dependent metaplasia, and/or a BMDC associated cancer, comprising detecting the presence of a mesenchymal stem cell (MSC) or MSC derived cell in a test sample from the subject are routine

to one skilled in the art. As stated in *Forman*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

In view of the ample guidance provided in the specification and the references cited therein, and the extensive knowledge available in the art, the instant specification enables a person of ordinary skill in the art to make and use the methods without undue experimentation. Accordingly, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements and, therefore, respectfully request reconsideration and withdrawal of the foregoing rejection of claims 1-4, 13-22, 28-33, and 36.

SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

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Respectfully submitted,

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